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The real face of HIF1α in the tumor process

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It is well known that the hypoxia-inducible factor 1 α (HIF1α) is detectable as adaptive metabolic response to hypoxia. However, HIF1/HIF1α is detectable even under normoxic conditions, if the metabolism is altered, e.g., high proliferation index. Importantly, both hypoxic metabolism and the Warburg effect have in common a decrease of the intracellular pH value.

In our interpretation, HIF1α is not directly accumulated by hypoxia, but by a process which occurs always under hypoxic conditions, a decrease of the intracellular pH value because of metabolic imbalances. We assume that HIF1α is a sensitive controller of the intracellular pH value independently of the oxygen concentration. Moreover, HIF1α has its major role in activating genes to eliminate toxic metabolic waste products (e.g., NH_3/NH_4+) generated by the tumor-specific metabolism called glutaminolysis, which occur during hypoxia, or the Warburg effect. For that reason, HIF1α appears as a potential target for tumor therapy to disturb the pH balance and to inhibit the elimination of toxic metabolic waste products in the tumor cells.

Keywords: HIF1α, glutaminolysis, Warburg effect, hypoxia, normoxia, ammonium, metabolism, tumor

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The transcription factor hypoxia-inducible factor 1 (HIF1) has been described as one of the key prognostic tumor factors that is accumulated and detectable in response to oxygen deprivation. Under hypoxia, HIF1α will be not hydroxylated and therefore not degraded by the von Hippel-Lindau tumor suppressor protein.[1] As a consequence, HIF1α accumulates and dimerizes with HIF1β to form the transcription factor HIF1, which then activates a panel of target genes (e.g., GLUT-1, GLUT-3, CAIX and VEGF).[1] HIF1/HIF1α appears to be an essential protein for an adaptive metabolic response to hypoxia for the survival of tumor and non-tumor cells.[2]

Under different but specific circumstances, including stress, growth factor application, oncogene activation (e.g., PI3K-Akt, Ras, Raf, Myc) or the density of cell cultures; however, HIF1/HIF1α is detectable even under normoxic conditions.[1,3-7]

However, the following questions remain: Why is the hypoxia-inducible factor 1α even detectable under normoxic conditions, and what is the common cause for both the normoxic and hypoxic accumulation of HIF1?

There is a consensus that multiple factors pertaining to the microenvironment, such as the local pH and metabolite concentrations, modify hypoxia-responsive protein expression.[8-11]

It is well known that a normoxic HIF1 accumulation can be induced by growth factor stimulation (e.g., insulin or EGF), which induces proliferation and modified cell metabolism.[5,6,12] Nevertheless, the growth factor-induced normoxic accumulation of HIF1/HIF1α is not caused by a direct response to oxygen deprivation. Rather the application of insulin can increase the local concentration of intracellular oxygen in a tumor cell.[13] This finding is a first example of a general oxygen-independent accumulation of HIF1.

Furthermore, metabolic intermediates have an impact on the accumulation of

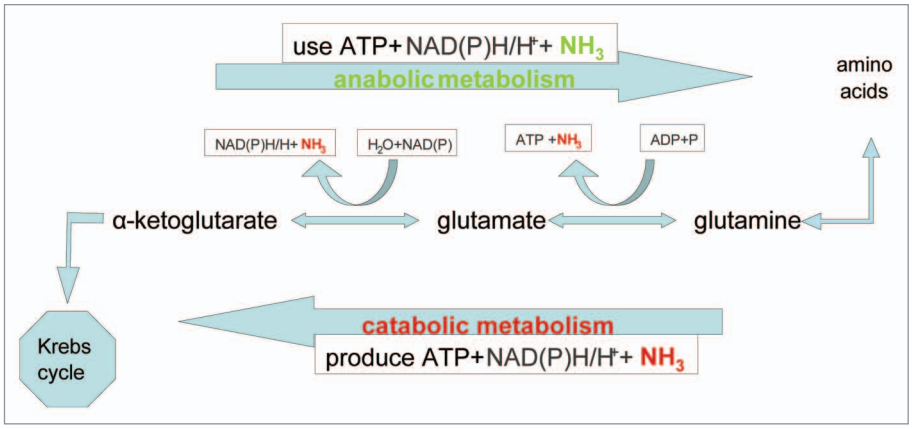

Figure 1. Part of the glutaminolysis pathway: Release of toxic ammonia during catabolic glutamine/glutamate degradation and importance of α-ketoglutarate as the acceptor of ammonia during anabolic metabolism. The intracellular concentration of α-ketoglutarate and ammonia are the key regulators for nitrogen metabolism, pH_i value and HIF-accumulation. HIF1 is the molecular sensor and regulator of the intracellular pH value.

HIF1. Fumarate and succinate, two citric acid cycle intermediates, cause a stabilization of HIF1α in fumarate hydrogenase and succinate dehydrogenase-deficient tumors.[14] Moreover, Kwon and colleagues have postulated that glutamine or glucose deprivation inhibits the accumulation of HIF1/HIF1α under hypoxic conditions.[8] Altogether, these findings indicate an important impact of an adaptive metabolic response on HIF1 accumulation that is independent of oxygen deprivation.

The crosstalk of HIF1 and the glucose metabolism in the context of the Warburg effect[15] was demonstrated in detail.[16] Denko assumed that normoxic/hypoxic accumulation of HIF1 is a benefit to the tumor not by increasing glycolysis, but by decreasing mitochondrial activity. The reduced mitochondrial function yields an increase of anabolic substrates because of an increased glucose uptake of the tumor cell and a decreased consumption for energy generation.[16]

On the other hand, increased anabolic substrates can be also generated by incorporation of glutamine in the tricarboxylic acid cycle as a carbon source.[16,17] Both glucose and glutamine are rapidly consumed during proliferation of most cancer cells.[17]

Under normoxic conditions, the metabolism of glutamine (glutaminolysis) is a major part of the Warburg effect.[18] A high consumption of glutamine seems to be a general phenomenon during the rapid proliferation of most cell types.[17] Glutamine is usually used as a nitrogen carrier to eliminate NH_3/ NH_4+ out of the cells. Tumor cells especially use glutamine as a metabolite. This finding is remarkable, because glutaminolysis is performed by cells under normoxic, hypoxic and even under anoxic conditions.[19] Strikingly, DeBerardinis et al. have found that most of the α-nitrogen from glutamine degradation was secreted from the cells as ammonia and alanine.[17] Other authors have described the importance of glutaminolysis and have suggested that the Warburg effect may be a metabolic consequence secondary to nitrogen anabolism (glutaminolysis).[20]

Therefore, Dang et al. have concluded that glucose metabolism (glycolysis) is insufficient to sustain a growing and dividing cancer cell. The Warburg effect requires glutamine for both redox balance and lipid synthesis.[21] By rethinking the Warburg effect, the amino acid glutamine seems to be very important for tumor cells.[18,22,23] An important consequence of glutaminolysis and the release of ammonia is a decrease of intracellular pH value (pH_i).[24,25]

However, hypoxia always decreases the pH_i value of the cell because of an alteration in the metabolic response (e.g., lactate and ammonia generation).[26-29] Recently, Ward and Thompson ascertained that altered metabolism by itself can be oncogenic and might be a hallmark of cancer.[30] Most toxic metabolic waste products generated by an overstimulated/altered metabolism by the Warburg effect or hypoxia have to be neutralized by the cell because of an increased risk of new oncogenic alterations.

Especially in the context of the HIF1 level, the impact of different factors like cMyc, STAT3, mTOR, p53/MDM2 on the Warburg effect and glutaminolysis should by further investigated.[12,31-37] The fact that HIF1 is involved in mitochondrial autophagy processes and, in this case, in the regulation of mitochondrial respiration is important.[2,38] It seems that HIF1 help to reduce the amount of toxic metabolic waste products, which should have an effect on the lifespan of cells or of a whole organism too.[39]

Role of HIF1 in pH Regulation

We suggest that the regulation of HIF1 is not directly caused by oxygen deprivation but by a change in the pH_i value and by a change in the equilibrium of intracellular ions. We assume that HIF1 is a sensitive controller of the intracellular pH value independently of the oxygen concentration. We think that the metabolic glutaminolysis pathway could be the main regulator/pacemaker for the accumulation of HIF1. A change in the pH_i value can be caused, for example, by the higher ammonia/ammonium concentration generated by the metabolic desamination of glutamine and/or glutamate during glutaminolysis, which occurs during the Warburg effect or even under hypoxia. It is understandable that a tumor-specific altered metabolism, which consumes the important nitrogen carrier glutamine, generated high concentrations of the very toxic metabolic waste product NH_3. Even tumor cells have to find a strategy to eliminate such toxic substances, immediately.

Experiments have demonstrated that ammonium supplementation causes a brief, initial intracellular alkalinization, followed by a rapid acidification.[24,26] Intracellularly originated metabolic ammonium ions are rapidly excreted to the extracellular space, which causes the intracellular accumulation of one proton (H^+) per NH_3 molecule released.[24,25] Because of this, the intracellular pH value reaches a new, lower steady-state value, a value at which the former

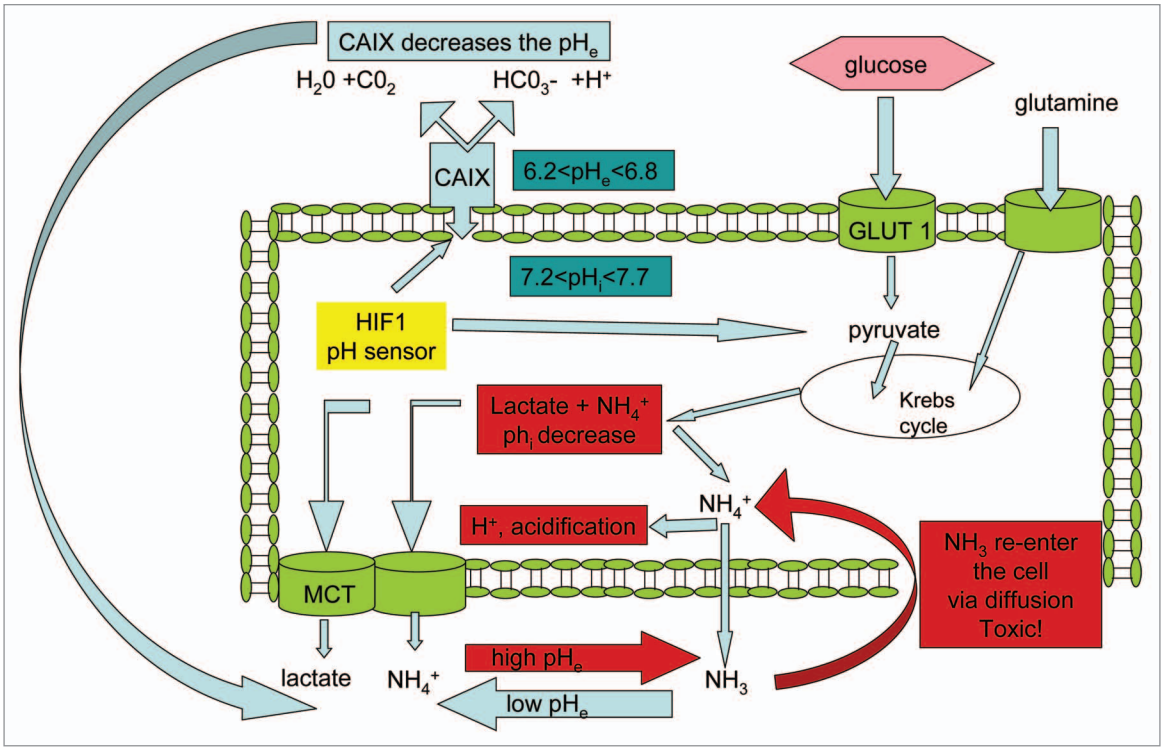

Figure 2. The elimination of ammonia/ammonium out of the cell would be facilitated by the HIF1-induced activation von CAIX. CAIX causes an extracellular acidification and milieu in which ammonia can be protonated to ammonium. At a higher extracellular pH value (pH$_e$), more ammonia can re-enter the cell and cause an intracellular acidification. The HIF1-induced GLUT-1 activation lead to an activation of glycolysis, a supply of the citric acid cycle with α-ketoglutarate and an anabolic metabolism (α-ketoglutarate and ammonia are converted to glutamate as shown in **Fig. 1**).

equilibrium between the H^+ and OH- ions is disturbed. The proton concentration is increased, whereas the OH- ion concentration is massively decreased and partly replaced by the basic molecule, NH_3/NH_4+ (pk$_s$ = 9.2). However, even a lower steady-state pH value is critical for the cells if the concentration of NH_3/NH_4+ further increases. Ammonia can diffuse across all membranes but will be protonated to ammonium at a lower pH value, such as in lysosomes. Such a mechanism is toxic, because ammonium cannot diffuse out of the cell compartment and induces functional inhibition of processes in the lysosomes, including iron metabolism.[40] Notably, even slight changes of the pH$_i$ could be harmful: a decrease of 0.2 in the pH value is sufficient to deactivate phosphofructokinase completely.[26,41]

For this reason, it is essential for the survival of the cell to stabilize the pH$_i$ rapidly and to reduce high NH_3/NH_4+ concentrations, because toxic intermediates, such as ammonia/ammonium, and changes in the pH value are detrimental even to tumor cells.

We propose that HIF1α/HIF1 is the key indicator and regulator of high concentrations of ammonia/ammonium and is a sensitive controller of the intracellular pH value. We suggest that a high intracellular H^+ concentration is pivotal for the lack of hydroxylation of HIF1α, as has been discussed by Chiche and colleagues.[26] This indicates that the common reason for both the normoxic and hypoxic accumulation of HIF1α/HIF1 is the need to regulate the pH$_i$ value, which is essential for cell metabolism.

Which Functions of HIF1 Support our Interpretation?

First, HIF1 can convert the catabolic metabolism of amino acids (glutaminolysis) to an anabolic process (e.g., α-ketoglutarate and ammonia are converted to glutamate). This can be achieved by the activation of glycolysis, which can generate NADP(H) as well as ATP, but can also supply the citric acid cycle with metabolic substrates. The activation of glycolysis can be induced by GLUT1 or GLUT3, transcriptional targets of HIF1.[1,26,27,42] GLUT1 increases the concentration of intracellular glucose, and an increase in the glucose concentration is also indicated for patients who suffer from hyperammonaemia. The acute hyperammonemia (more than 500 μM NH_4 in blood) is treated by a high amount of glucose to alter the catabolic conversion of amino acids to an anabolic conversion. The described paradox that catabolism and anabolism can coexist in the case of hypoxia[26] can be explained by our interpretation of the function of HIF1.

Second, ammonia/ammonium has to be transported out of the cell. Ammonium can be actively removed by the Na^+/NH_4+ and Na^+/H^+ co-transporters.[26] The excretion of NH_4+ creates a persistent acid load on the cells and is facilitated by the negative charge of the membrane potential and the gradient of ammonia across the cell membrane.[24,25] However, a pH-dependent amount of extracellular free ammonia (1% at a pH value = 7.2, 2% at a pH value = 7.4) remains.[24] Once outside of the cells, the ammonia can re-enter the cells

over and over again, because NH_3 passively diffuses across the membrane and can be protonated only at lower pH values.[24,25] To block the re-entry of NH_3, the cells have to decrease the extracellular pH value, which will result in the protonation of NH_3 to NH_4+, because NH_4+ cannot enter the cell by diffusion.

To achieve a decrease in the extracellular pH value, CAIX can be activated by HIF1. CAIX decreases the extracellular pH value by the hydration of CO_2, which generates an extracellular proton and contributes to extracellular acidification.[1,26,27]

Third, cells have to react immediately, if the intracellular pH value is changed or toxic metabolic waste products were accumulated. The HIF1 system is geared to react within minutes.[1] Following our interpretation, it is understandable why the HIF1 system must be a very quick adaptive control system of cells, because metabolic imbalances are critically for survival even to tumor cells.[43] However, if the HIF1 system really induce the oxygen availability by influencing the neoangiogenesis via, e.g., VEGF activation,[1] which needs at least days, the HIF1 system ought to react less quickly than it seems to. This is at least a question about the logical behavior of a biological system.

Conclusion and Future Perspectives

We assume HIF1α/HIF1 is not directly accumulated by hypoxia, but by a process which occurs always under hypoxic conditions, a decrease of the intracellular pH value. We suggest that HIF1α/HIF1 is an indicator and regulator of high concentration of ammonia/ammonium and a sensitive controller of the intracellular pH value. In that case, HIF1α/HIF1 is an indicator of the Warburg effect, too.

In this context it appears that all of the HIF1 target genes (e.g., VEGF, GLUT1, GLUT3, CAIX) are more likely involved in the rapid regulation of the pH_i value than in the fast regulation of the intracellular oxygen concentration. Our hypothesis contrasts with the general interpretation of the function of HIF1α/HIF1 as an indicator/regulator of the intracellular oxygen concentration.

However, the logical discrepancy between the activity and the occurrence of HIF1α/HIF1 under both hypoxic and normoxic conditions can be solved if we consider HIF1α/HIF1 as an indicator and regulator of the intracellular pH value/ion equilibrium.

In addition, acidic tumor environment could be a good target for tumor therapy, because the acidic milieu is essential to eliminate the toxic molecule ammonia/ammonium out of the tumor cell. Inhibition of HIF1 and/or HIF1-target genes could be a strategy and therapeutic approach, which causes an accumulation of toxic metabolic waste products (e.g., ammonia/ammonium) generated by the tumor-specific metabolism (Warburg effect or hypoxia) to poison the tumor. [**Fig. 2** adapted from Chiche et al. *J Cell Mol Med* 2010; 14:771-94 (Fig. 7)].

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